Bacterial Endocarditis: The Process of Healing

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ALTHOUGH bacterial endocarditis has been recognised as a separate disease entity since Ormerod (1851) described the vegetations of bacterial endocarditis and showed how they differed from rheumatic verrucæ, several problems remain unsolved. Following the advent of the sulphonamide drugs and the antibiotics, the problems in connection with healing have become increasingly important. In the later 1940's the proportion of treated cases reaching a successful issue gradually increased, but failures still occur. A lack of careful preliminary bacteriological investigation and carelessness with the details of treatment would appear to account for some of the failures, but a considerable number remain unexplained. With these considerations in mind, it appears important to study the cellular process of healing.

MATERIALS AND METHODS.

The post-mortem records of the Institute of Pathology of Belfast, from January, 1938, to January, 1950, were used to provide material for this study. The series included both treated and untreated cases. As the treated cases did not differ greatly from the untreated ones, the stages of healing observed will be described, followed by a discussion of the effects of treatment.

Material from eighty cases was available for histological study. In the majority of instances, the blocks of the vegetations were recut, and in many cases sections at different levels were prepared. When signs of healing were present, serial sections at various levels were studied. The original sections were stained with hæmotoxylin and eosin, and where it was considered necessary this was supplemented by one or more of the following stains : a combination of Weigert's elastin stain with van Gieson's connective tissue stain; Masson's trichrome stain; Brown's modification of Gram's stain for bacteria; and von Kossa's stain for calcium.

RESULTS.

In the material of this study there were several examples of very early bacterial vegetations. These consisted of small masses of fibrin and bacteria, in which there were no traces of elastic tissue, situated directly on the surface of the valve. There was an early infiltration of inflammatory cells in the underlying valve. In larger vegetations the basal part of the lesions often contained strands of elastic tissue. It is thought that as the bacteria multiply, they ulcerate the substance of the valve, so that remnants of valve tissue come to be present in the basal part of the vegetation.

In the majority of these cases, bacteria could be identified in sections stained with Brown's stain. In a few cases in which the lesion was healing or healed, no

bacteria could be seen in the sections. The evidence will be presented for believing these cases to be examples of healed bacterial endocarditis.

Process of Healing. A proliferation of fibroblasts at the base of the vegetation was present to some degree in 63 per cent. of the cases studied. In those instances where there were well-marked attempts at healing, it could be seen that the proliferation of fibroblasts at the base, and especially at the margins, must have played an important part in the process of repair. It was sometimes present in early lesions, even in those which appeared otherwise destructive. It was present in vegetations from cases where the total duration of the illness had been less than three weeks, yet it was absent in one with an illness of three months. It was very marked in a case which had a perforation of the valve cusp. It was present to a marked degree in those cases where there was further evidence of healing.

This proliferation of fibrous tissue at the base of otherwise active vegetations was often accompanied by the formation of new capillaries, and, in some cases where healing was advanced, this was a prominent feature. Since fibroblasts were some times seen without recognisable capillaries, it was thought that the fibroblasts preceded the capillaries. Eventually a layer of granulation tissue was formed similar to that seen in association with inflammatory lesions in other parts of the body. When the vegetations were small, consisting mainly of fibrin, with few bacteria, it seems as though the advancement of this tissue gradually replaced the vegetation so that there remained only a pad of granulation tissue (Fig. 1). In several cases microscopic granulomata were seen on the heart valves and in the valve angles. Many hæmosiderin-containing macrophages were present in these lesions. There was no proof that they were of bacterial origin, but there was considerable evidence in support of this view. In one instance there were active bacterial vegetations on the other cusps of the valve. Lesions of this type have never been described as a result of rheumatism. They bear a close resemblance to bacterial lesions in other parts of the body.

This gradual replacement of the vegetation by granulation tissue did not appear to play a prominent part in the healing of larger vegetations. In such lesions the first important stage appeared to be the growth of endothelial cells from the adjacent endocardium over the surface of the vegetation. The endothelial cell layer was single at first and the cells were separated from the bacterial colonies by a layer of fibrin. In some cases this fibrin layer was very thin. This was present as early as twenty-three days after the onset of symptoms. The endothelial cells were derived from the adjacent healthy endocardium. They were large and active-looking, and spread gradually over the surface of the vegetation. Fibroblasts followed the endothelial cells over the surface of the lesion. This was usually, but not always, accompanied by the invasion of the base by fibroblasts. Various stages in the formation of a complete fibrous tissue capsule were seen. This process of encapsulation was sometimes present in lesions which were advancing in other areas. Bacteria which stained deeply with Brown's stain were occasionally present within completely encapsulated vegetations, showing that encapsulation can occur before the bacterial colonies are killed. In other lesions the centre consisted of necrotic material and

nuclear debris, without identifiable cells or bacteria. This process of encapsulation of the vegetation with fibrous tissue was considered to be an important stage of healing, as it indicated that the defences of the body were in the ascendant, even if only temporarily and locally.

Capillaries followed the fibroblasts over the surface, and eventually the vegetation became covered with a thick layer of granulation tissue, similar to that present at the base (Fig. 2). Hæmosiderin-containing macrophages were present within this capsule. Occasionally there were multi-nucleated giant cells of the foreign body type. In a few instances small masses of bacteria and fibrin, together with acute inflammatory cells, were seen beneath a layer of old collagenous fibrous tissue. The fibrous tissue was relatively acellular and was thought to be older than the bacterial lesion. This was considered to be the result of active bacterial lesions extending into an area of old fibrous thickening of the valve, and not a part of the process of repair.

There were numerous examples of partially and completely encapsulated vegetations. The centre of the vegetation was composed of necrotic inflammatory cells, dead and dying bacteria, and old fibrin. The necrotic material remained for a considerable time, and was sometimes present in lesions when collagen was present in the capsule. There were sometimes deposits of calcium in this core, even in relatively young lesions, when the bacterial endocarditis was advancing in neighbouring areas (Fig. 3).

These stages can be followed in vegetations where there is good evidence of bacterial origin. Bacteria can be identified even when calcification has commenced. Once the bacteria have disappeared we are faced with the problem of the interpretation of a scar. It is conjectured that the vascular channels gradually disappear and most of the hæmosiderin-containing macrophages are carried away in lymphatics. As this occurs, the scar loses its specific characteristics and becomes merely a mass of calcium buried in relatively avascular fibrous tissue. In this series there were three cases in which there were calcified vegetations of this type, associated with evidence which was strongly suggestive of bacterial endocarditis. There were several other cases in which histologically similar lesions were present, but without history or other evidence to suggest bacterial endocarditis. As their ætiology could not be decided, they have not been included in this series. Secondary calcification of an old area of rheumatic fibrous thickening of a valve cusp could produce an appearance similar to healed vegetations of bacterial endocarditis.

Examples of Healed Bacterial Endocarditis. Three male patients had a history of rheumatic fever many years before their final illness. In each case the streptococcus viridans had been isolated from the blood stream on two or three occasions. They improved with penicillin therapy, but after a period varying from six weeks to three and half years they died from congestive heart failure. At autopsy all had healed infarcts in the brain or abdominal viscera. There were healed vegetations on the mitral valve, in two cases associated with ruptured chordæ tendineæ. The larger vegetations consisted of masses of calcium buried in collagenous fibrous

tissue. In one case numerous blood vessels and crystals of hæmosiderin were present (Fig. 4). Bacteria were not present.

Effect of Treatment. In this series of cases twenty-nine received chemotherapy and/or penicillin therapy; forty-three cases were untreated; there was no information as to treatment in eight cases. The stages of healing which have been described can be found in the untreated, as well as in the treated cases, with the exception of the calcified scar. The more advanced stages of healing appeared more frequently amongst the treated cases, as one would expect, and the three cases which have been regarded as examples of completely healed bacterial endocarditis had received penicillin treatment. Healing tended to progress more rapidly in the treated cases, but even in these instances bacteria remained stainable within the vegetations for long periods. The difference between treated and untreated cases was not sufficiently striking to enable one to pick out the treated cases.

In both treated and untreated groups there was little relationship between the degree of healing and the duration of symptoms (the presumed age of the vegetations). Well-defined attempts to encapsulate the vegetations were seen in cases with symptoms for twenty-three and thirty-five days respectively, although no treatment with sulphonamides or penicillin had been given. A treated case with symptoms for thirty days had similar partially encapsulated vegetations. In another untreated case this process was only beginning after six months.

Bacteriology. A micro-organism was isolated in thirty-five of the eighty cases studied. In twenty-five cases the organism was recovered from the patient's blood stream during life. In eight cases bacteria were cultured from the vegetations and/or the spleen at post-mortem. However, Wright (1925) and Epstein and Kugel (1929) regarded post-mortem cultures as of doubtful significance. The latter workers isolated streptococci in 40 per cent. of cultures taken from normal valves.

In only two cases in the present series was the same organism recovered at post-mortem as had been obtained by blood culture during life. The Streptococcus viridans was isolated in eleven cases, the Staphlococcus aureus in ten, the Staphlococcus albus in three, the Streptococcus hæmolyticus in three, the Hæmophilus influenza in three, and the Pneumococcus in five.

When the degree of healing was compared with the casual organism, it was interesting to note that, in general, there were few or only slight signs of healing in the vegetations due to pyogenic organisms. Occasionally, however, a vegetation from which a pyogenic organism had been isolated showed more advanced healing than some of the vegetations due to the Streptococcus viridans.

Discussion.

It will be noticed that there has been no attempt to classify this series of cases into acute and subacute bacterial endocarditis. It was found unreliable to divide the cases into these two types on a basis of duration of symptoms, especially as the disease has typically an insidious onset. In some instances patients died from embolization or intercurrent infection early in the course of the disease, yet histological examination of the vegetations revealed well-marked proliferation of

fibrous tissue at the base and attempts to cover the surface. On a basis of time alone, these cases would have been classified as examples of acute bacterial endocarditis. It seems unsound to regard as subacute all those cases where the endocarditis appears to be the primary infection, and to reserve the term acute for those in which a primary infective process has been found in another organ. Cases were examined where the vegetations were of the destructive ulcerative type, yet no other infective process was found. Healing vegetations were seen in a case where the endocarditis was a secondary lesion. It was concluded that the disease should be called bacterial endocarditis, adding the name of the casual organism, where it is known, as a prefix.

The Healing of Bacterial Vegetations. The first favourable reaction of the valve to the presence of the bacteria, apart from an infiltration by inflammatory cells, appears to be a proliferation of fibroblasts at the base of the vegetation. It was present in 63 per cent. of the cases studied, but in the majority of them the attempt to heal the lesion had not proceeded further. In most instances it appeared as though the body's defence mechanism was unable to hold the infection in check while the process of healing continued. Some times a cerebral embolus or an episode of intercurrent infection terminated the life of the patient. The presence of fibroblastic activity did not appear to be related to the duration of the symptoms (although this appears to be an unreliable criterion for the age of the infective process, since the disease is notoriously of insidious onset). It was present in a number of cases which had not received chemotherapy or antibiotic treatment. It was impossible to exclude a varying degree of virulence of different organisms, or even of different strains of the same organism, but even this factor did not appear to account for its presence or absence. Occasionally a vegetation from which a pyogenic bacterium had been isolated showed more advanced healing than some of the vegetations due to the streptococcus viridans. It was thought that the importance of the fibroblastic proliferation lay in the fact that it showed that the patient had the power to react to the bacterial process. More extensive repair might have been achieved if the patient had survived for a longer period.

The first definite stage of healing appeared to be the proliferation of the cells of the healthy endocardium adjacent to the vegetation. These cells extended over the vegetation on a layer of bacteria-free fibrin, which formed the periphery of the vegetation. The endothelialization of a bacterial vegetation is of great importance in the process of healing. As long as the vegetation remains in open communication with the blood stream, the fibrin portion of it offers an ideal culture medium for bacteria carried to it by the blood stream. Even if the interior of the vegetation becomes sterile, the outer surface remains adhesive, so that chance bacteria might easily adhere to it and give rise to a fresh episode of infection. With the formation of a smooth endothelial covering, the adhesiveness disappears, and there is a consequent decrease in the danger of reinfection. Treatment ought to be continued at least until the surface of the vegetation is completely covered with endothelium.

The formation of a fibrous tissue capsule by the growth of fibroblasts following the endothelial cells over the surface of the vegetation appears to be the next stage

of healing. Capillaries followed the fibroblasts to form a capsule of young granulation tissue. It was interesting to observe that one part of a vegetation might be covered in this way, while the bacteria were advancing in a neighbouring area. Nevertheless, there were some vegetations in which the bacteria appeared to be non-viable in some areas (as judged by post-mortem culture and staining reactions), yet no attempt to cover the dead colonies had occurred.

As the fibrous tissue capsule was forming, fibroblasts were growing into the base of the vegetation, anchoring it firmly to the valve. The possibility of fragments of the vegetation becoming detached and the formation of emboli were more remote. There was no significant difference in the occurrence of embolization in the treated and untreated cases in this series.

After the vegetations had become encapsulated, the bacteria tended to lose their staining reactions, and were considered to be no longer viable. It was noteworthy that this stage might be delayed until the capsule had become adult fibrous tissue, and most of the inflammatory cells had disappeared. The long survival period of bacteria within healing vegetations has an important bearing on the time for which treatment should be continued. As long as bacteria which stain well remain within the vegetation, a recrudescence of infection may be possible, and treatment should be continued until this danger is past. Christie (1948) reported deeply staining bacteria in the vegetations of thirteen out of thirty-nine apparently controlled cases. Knowledge of this does not help in determining the duration of treatment in the individual patient, but it indicates that a prolonged course of treatment would be more likely to give good results than a short course however high the dosage. This is in agreement with the findings of clinical investigators (Christie, 1948; Donzelot, Kaufman and Escalle, 1947).

The mass of material forming the core of the encapsulated vegetation, consisting of necrotic material and dead bacteria, appeared to shrink a little and calcium salts were deposited within it. It is interesting to note that this sometimes occurred even in vegetations in which the bacteria still stained deeply, and there were numerous polymorphonuclear cells in the surrounding fibrous tissue. Once the centre of a bacterial vegetation becomes infiltrated with calcium, the shape and the size of the scar is fixed, and if it is large there results a considerable deformity of the valve on which it is situated. In very small vegetations the advance of granulation tissue from the base appears to replace the vegetation without the deposition of calcium salts, presumably because the amount of necrotic material is small and can be carried away by phagocytes. Where there is a large mass of necrotic material, only the fringe of it is accessible to the action of the phagocytic cells. The replacement of the vegetation by granulation tissue ought to result in less deformity of the valve cusps. From a pathological point of view, as well as a clinical one, early diagnosis and treatment, while the vegetations are still small enough to be healed in this way, seems to be essential to obtain a good functional result.

Some of these stages of healing have been described by other workers. Libman (1912) described masses of calcium embedded in relatively avascular fibrous tissue

situated on the heart valves. They were associated with healed perforations of the cusps and with healed Lohlein's lesions in the kidneys, and he believed them to be examples of healed bacterial endocarditis. Moore (1946) studied the healing process in cases of bacterial endocarditis which had been treated with penicillin, and he described the covering of the vegetations with fibrous tissue, and the partial removal of the necrotic material by phagocytes, followed by the deposition of calcium salts in the remaining necrotic material. He described a final stage in which clefts appeared in the vegetation and became lined with endothelium, to form a spongework of blood channels, which he considered was pathogonomic of bacterial endocarditis. This spongework was not seen in the material forming the present study. His study was carried out on twenty-two treated cases of bacterial endocarditis, with eight untreated cases as controls. He found some evidence of healing in the control cases, but it was more advanced after treatment with penicillin.

From the present study it appeared that the most important factor influencing the degree of healing was neither the age of the lesion nor the treatment received. The micro-organism causing the disease appeared to be of great importance apart from differences in sensitivity to chemotherapy and antibiotic treatment. If the organism was of sufficient virulence, then the patient died early in the course of the disease, and the treatment did not appear to affect the issue. In the group of cases which survived longer, usually due to the Streptococcus viridans, there were widely differing stages of healing. It was thought that this could only be accounted for by assuming some differing power of tissue response in the individual patient. Many factors might influence the tissue response, for example, the state of nutrition of the patient and the effect of bacterial toxins from the heart lesion. In the present state of our knowledge it would appear that general measures of good nursing and attention to the state of nutrition of the patient still have an important place in the treatment of bacterial endocarditis.

Summary.

1. The findings of a study of eighty cases of bacterial endocarditis have been described.

2. The healing of bacterial vegetations occurs in the following stages :—
   - I. Invasion of the base by fibroblasts and young capillaries.
   - II. Endothelialization of the surface.
   - III. Formation of a fibrous tissue capsule.
   - IV. Death of bacteria.
   - V. Calcification of the necrotic centre of the vegetation.

3. It is suggested that the accepted classification of bacterial endocarditis into acute and subacute types does not serve any useful purpose, and it is proposed that the disease should be called bacterial endocarditis, qualifying this where possible with the word healing or healed, and the name of the casual organism.

4. The treated cases are compared with the untreated, and it appears that while the healing may be facilitated by treatment, the essential nature of the process of healing is not altered.

5. There is no apparent relationship between the presumed age of the vegetation and its histological appearance.

6. Less advanced healing, in general, occurred in vegetations due to pyogenic organisms, while healing had progressed further in those due to the Streptococcus viridans.

7. It is suggested that the tissue response of the individual has an important bearing on the degree of healing achieved. This might be influenced by the state of nutrition of the patient, and by bacterial toxins produced by the bacteria causing the disease.

8. It is essential to diagnose and treat bacterial endocarditis while the vegetations are still small, if a good functional result is to be obtained. Treatment should be very prolonged since apparently viable bacteria can persist for long periods in the middle of healing vegetations.

References.

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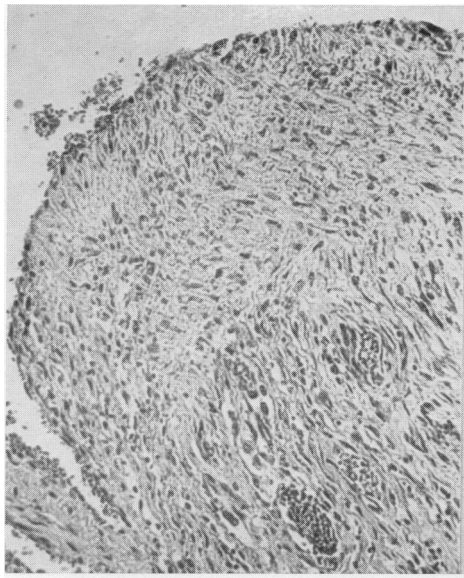

Fig. 1.

A 6612 H. and E. ×140.
Microscopic granuloma in the mitral valve angle.

Fig. 2.

A 3154 H. and E. ×92.
Thick layer of granulation tissue covering a bacterial vegetation.

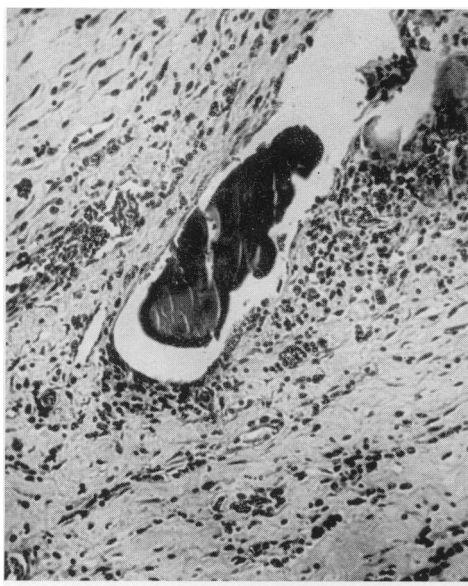

Fig. 3.

A 6530 H. and E. ×140.
Calcium in vascular granulation tissue at the base of a bacterial vegetation.

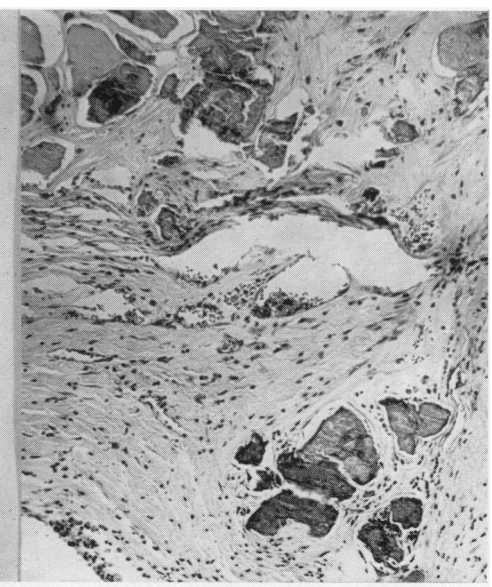

Fig. 4.

A 6242 H. and E. ×90.
Masses of calcium, embedded in fibrous tissue—completely healed bacterial endocarditis.